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Non-Conventional Approaches to *In-vivo* Drug Tracking and Targeting - A Review

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ABSTRACT:
The drug molecule produces specific action on targeted tissues or organs to normalize their biological functions. The drug molecules in specific tissues or organs has important role in diagnosis or prevention of disease in human. The drug molecules can be designed with structure based or ligand based drug designing methods. In addition, the drug molecules in targeted tissues or organs can be detected by non-conventional techniques. This review summarizes about drug designing and non-conventional drug imaging techniques such as Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Near Infra Red (NIR) spectroscopy along with magnetic based technology, nanotechnology, Bio-MEMS and laser technology. The present review indicates the potential role of non-conventional drug imaging techniques to detect the targeted drug molecule.

Keywords: Drug designing, Drug targeting, Non-conventional Techniques

INTRODUCTION

Drug is a chemical substance, used for the prevention or diagnosis of disease or to enhance the physical or mental well being. When they are absorbed in the body they alter the normal functions of the body [1]. Sometimes drugs are used to give pleasurable sensations and are called recreational drugs. A simpler definition of drug can be given as a chemical substance that affects the body and its processes [2].

DRUG DESIGNING

Drug designing is also known as rational drug design and is a method of finding medications based on the target molecules such as biological receptors. The basic step involves in designing of such molecules that are complementary to the biological targets to which they interact and bind thereby causing the pharmacological effects [3**]**. Drug designing mainly concentrate on ligand designing. In drug designing, drug should have the following properties like, it should lack the toxicity and it should obey the desired pharmacokinetic activity (said by IUPAC commendium). It is the process of finding new medicine, based on the knowledge of specific target molecule such as protein to which the designing drug will bind. The drug molecule will activates or inhibits the function of the biomolecule such as a protein which will results in the therapeutic benefit [4].

STRUCTURE BASED DRUG DESIGNING

The interaction of small molecule (drug) with a three dimensional structure of the target at specific site, happens in structure based drug discovery. The whole process is used as a guide to discover a new drug. In this method of drug designing we can exactly visualize how our drug interacts with the target protein.

Some techniques like, X-ray crystallography and Nuclear magnetic resonance spectroscopy (NMR) helps to know the structural information. NMR is a comparatively slow method in structure prediction than crystallography and 3-D structure cannot be predicted for proteins larger than 30,000 Da [5].

Structure based drug designing is a method of developing a new molecule from its initial state. It is compared with *de novo* method of synthesizing a complex molecule. Drug molecule should interact with target molecule at the right site and perform a right function and that is the most important aim in drug designing. The lead compounds are identified by screening and *de novo* design. This has been performed to improve the potency and specificity of the lead component. Lead optimization is one of the driving forces behind structure based drug designing method. This explains how a lead compound will quickly bind to the target molecule. By this method we can improve the binding affinity of our desired molecule (drug) easily.

LIMITATIONS OF STRUCTURE BASED DRUG DESIGNING

In this method are in quantitative prediction of the lead molecule's modification in binding, complexity of drug binding process and the conformational response of macromolecular structures to ligand binding cannot be accurately predicted.

The estimation of effects due to the factors such as polarizability, salvation and enteropy that may have an important influence on drug binding energetics cannot be estimated accurately. But computational design shows many improvements in structure based drug designing [6].

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LIGAND BASED DESIGNING

Ligand based designing depends on two dimensional or three dimensional chemistry, shape, electrostatic properties and interaction of both the drug and the target molecule. Ligand based drug designing approach need much less information than structure based drug designing. It needs knowledge only on active molecules. The molecules that bind with the active site of the target molecules are selected and those molecules that can bind with the prior molecule is selected and added. By this way the drug molecule is developed. When a molecule bind with the target receptor it exerts some effect or conformational changes on the receptor in a three dimensional manner. If the conformational changes are observed to be positive for the desired action (may be inhibitor or activator) of the drug then the molecule is selected as a drug [7].

ADVANCED IMAGING TECHNIQUES

Medical imaging or nuclear medicine is based on detecting the nuclear radiation emitted by radiolabelled drugs inside the body. The basic requirement for imaging is radiation and these radiations are readily assessable [8].

TYPES OF IMAGING TECHNIQUES

There are two types of imaging techniques:

i. Conventional method
ii. Non-conventional method

Conventional method

In many former methods the detection of drugs are done by assays of enzymes or monoclonal antibodies. A first step improvement was given by using mobile devices to detect the drug in saliva and other fluids. These are more costly so large amount of money have to be spent to test the sample. Electronic monoclonal antibodies or immunosensors need well trained user. In the year of 2008, a new approach for testing the drug for the road side analysis was detected. In this method ultraviolet fluorescence is used. The method used two compounds to check. The first compound will absorb and generates UV radiations that are absorbable by the drug. The second compound will absorb UV radiation absorbed drug that can be detected by spectrometry [9].

Non-Conventional methods

Several non-conventional modalities having applicability are

- Single Photon Emission Computed Tomography (SPECT)
- Positron Emission Tomography (PET)
- Magnetic Resonance Imaging (MRI)
- Near Infra red (NIR)
- Magnetic targeted carrier Technology
- Nanotechnology
- Bio-MEMS technology
- Laser technology

SPECT

Single Photon Emission Computed Tomography (SPECT) is the *in vivo* method of imaging human body with the help of gamma radiation. Kuhl and Edwards produced first tomographs from the emission data in 1963 that paved the way to view human organs internally. It has undergone various changes in the hands of many scientists to obtain its best result in medical imaging.

The image given by SPECT is cross-sectional slices through the patients, which can be easily manipulated. One should obtain 3D images from the SPECT. Gamma-emitting radioisotopes in the blood stream of the patients are injected to view the drugs that have been coated with radioisotopes. The radioisotope should be in the form of simple soluble ions. The marker of the radioisotope should not alter the chemical nature of the drug or it should not alter the normal metabolic function of the body [10].

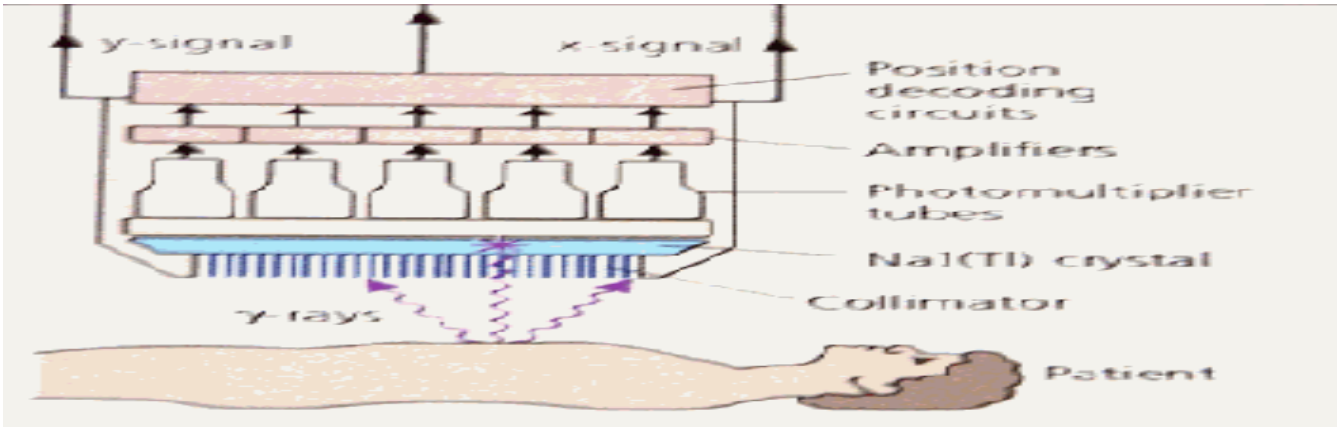

Fig1: Single Photon Emission Computed Tomography

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THERAPEUTIC APPROACHES USING SPECT

Radio isotopic assay developed for observing radio labeled drugs in the vertinary and food animals. The radio labeled drugs are characterized by mass spectrometry, nuclear resonance spectrometry and infrared spectrometry [11].

The Near-infrared absorption and scattering spectroscopy has been used to detect the limit of glucose. Skin layered models are used to perform the experiment. The result satisfied the requirement of food and drug administration of noninvasive glucose sensing [12].

The ocular spectrometer was constructed with a hand held sensor head. By placing the sensor head on the surface of the cornea, demonstration of real time, ocular drug detection in living eye using absorption spectroscopy is done. Brimonidine drug detection in cornea and anterior chamber of in vivo human and rabbit eye has been clearly demonstrated. It functions as an absorption spectroscopy and can be improved to fluorescence spectroscopy for pharmacological use [13].

Interactivity Laser Spectroscopy (ILS) sensor is used to detect narcotic drugs taken by a person. ILS is used to detect the presence of drugs and their metabolized by-product vapor in an enclosed space such as vehicle. It is also used as road side detectors to detect the presence of such drugs. Fluorescence microscopy imaging is used to study the dynamics behavior of microtubules of kidney in different drug dynamics. By this imaging the microtubules are detected and tracked [14].

SPECT experiment is performed to measure ketenserin dose dependent displacement in the cerebral region rich in 5-hydroxytryptamine sub type 2A (5-HT_{2A}) receptor. SPECT was performed on healthy individuals from the time of injecting radio iodinated 4-amino-N-1-[3-(4-fluorophenoxy) propyl]-4-methyl-4-piperidinyl] 5-iodo-2-methoxybenzamide (^{123}-R91150) until 470 minutes afterward. The dose dependent displacement of ketenserin in the cerebral region rich in 5-HT_{2A} receptors is measured using ^{123}I-R91150SPECT. Measurements of drug induced 5-HT_{2A} receptor occupancy in humans are done using SPECT ligand [15].

Accurate and reliable measurements of drug delivery to the lungs are done by inhaling radiotracers. Imaging those radiotracers through SPECT and PET is possible to take these measurements. Topical drug delivery to the lung remains the route of choice for administering drug therapy. Isotopes are mostly used as tracers for SPECT. 99m-technetium or pertechnetate ($^{99m}TcO4^-$) is often used isotope for SPECT. The half life of the isotope varies depending on the drug labeled for the specific test measurement. Some studies involve direct labeling of the drug. 123I-interleukin-1, 123I-interleukin-8 and the neuropeptide111 in-substance-p are small proteins and peptides as radiopharmaceutical agents, used for direct imaging of acute inflammation and infection through SPECT. SPECT imaging has an advantage that accuracy of assessing the pattern of drug deposition within the lungs [16].

Chemosensitivity of lung cancer to mitomycin C [MMC], and otoposide [VP-16] independently of Pgp [P-glycoprotein] expression can be predicted by the noninvasive *in vivo* examination of ^{99m}Tc-hexakis-2-methoxyispbutyl sonitrile SPECT images [^{99m}Tc-MIBI SPECT]. It has been reported that in various tumors the transport substrate for Pgp is 99mTc-MIBI and its accumulation is very high. In addition, Pgp expression and 99mTc-MIBI uptake and their relationship also explained. The usefulness of 99mTc-MIBI SPECT for *in vivo* assessment of lung cancer chemo sensitivity has been evaluated. These markers are also used for viewing various cancer images using SPECT [17, 18].

Presynaptic dopamine transporter (DAT) and postsynaptic dopamine D_2 receptor are striatal dopamine binding structure. The assessment of these simultaneous dopamine binding structures in first episode drug-naïve schizophrenic patients has been compared to healthy control person by dual-isotope SPECT technique. Functionally interrelated anatomic structures can be evaluated using *in vivo* dual-isotope imaging. The extent of delusions, conceptual disorganization and hallucinatory behavior has been demonstrated along with inverse correlation between DAT and D_2 availability. Significant higher DAT availability in patients with predominant positive symptoms was observed than the healthy individuals [19].

Penetrations of several diagnostic imaging agents are restricted by several barriers. They exist between blood and neural tissue, in the endothelium of parenchymal vessels (blood-brain barrier, BBB), epithelia of choroids plexus and arachnoid membrane. The snapshots SPECT on the cerebral perfusion using ^{123}I- and ^{99m}Tc-labelled lipophillic agents can be used to image delivery of diagnostic agents to the central nervous system. The agents that can reach plateau concentration of in the brain within 15-15 minutes after injection are used. They are lipophilic and freely diffusible across the (blood brain barrier) BBB and are used for SPECT imaging. Some commonly used agents are ^{99m}Tc-hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) and 99mTc-ethyl cysteinate dimer (^{99m}Tc-EDC). Cerebral perfusion can be calculated by the SPECT image obtained through these agents [20]. The molecular hallmark to select metastatic cancers is

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matrix metalloproteinase-14 (MT1-MMP or MMP-14). It is a membrane associated protease. The i*n vivo* detection of MMP-14 is good for studying its role in pathologic processes and its detection will be used as a guide for the development of targeted molecular therapies. MMP-14 sensitive probe for SPECT imaging has been made by the combination of design strategy and computational chemistry along with parallel synthesis and protease cleavage studies. It will be used to target the metastatic cancer and it will be viewed through SPECT images [21]. In the study of thermosetting ocular drug delivery system, SPECT is used for i*n vivo* or e*x vivo* evaluation of thermosetting gels. This thermosetting ocular drug delivery system is used to deliver ophthalmic drug, which will not make irritation of cold to the sensitive ocular tissues in to the eye at room temperature [22]. For the treatment of Parkinsons disease testing putative neuroprotective agent is the important one. The loss of presunaptic nigrostryatal projections in Parkinson's disease has been showed by ^{123}I-ß-CIT SPECT images. These types of several biomarkers are used in various therapies [23].

PET

Positron Emission Tomography (PET) is an imaging technique that produces three dimensional image in the body. It was introduced by David E Kuhl and Roy Edwards in 1950.

The imaging technique was further developed by Michel Ter-Pogossian, Michael E.Phelps. PET is used in both medical and research tool and is used in clinical oncology and diagnosis. PET is also used in pre-clinical studies in animals, mapping human brain and heart. PET imaging is performed by means of PET scanner and by means of gamma camera [24].

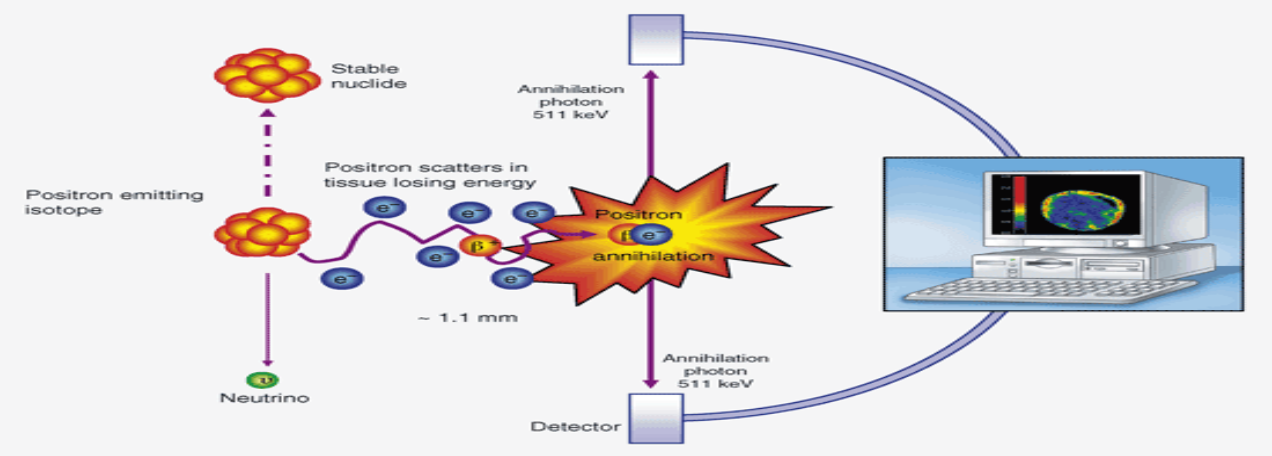

Fig2: Positron Emission Spectroscopy

THERAPEUTIC APPROACHES USING PET

Positron Emission Tomography was used as a research tool for the development of new drugs at lower costs. This is a powerful imaging technique and is used in designing dosage levels and regimens of Central Nervous System (CNS). The main use of PET is the imaging of the neuroreceptor a target binding site in the brain. The imaging of the neuroreceptors helps to study the relationship between the dose of drug administered and the receptor occupancy [25].

PET was used for imaging the nicotinic acetyl choline receptors (nAChRs) in the human brain to study their functions in normal and pathogenesis of brain disorders. The *in vivo* visualizations are carried out by means of PET and 2-[^{18}F] fluoro-3-2-(s) azetidinylmethoxy pyridine (2-[^{18}F] FA. The nicotinic acetyl choline receptors can be viewed in the thalamus after 5 hours of injection [26].

Positron Emission Tomography was used to observe the oral drug deposition in the gastro-intestinal tract and to observe the process of oral drug absorption. For hexose absorption PET probe used is 2-[18F] fluoro-2-deoxy-D-glucose [27]. PET was used to study the retention and spatial distribution of iododeoxyuridine (IUdR) a DNA-targeting radiosensetizing drug used in brain tumors. The drug was given intravenously and their distributions inside the various brain tissues are examined [28].

Drug development based on PET molecular imaging needs some additional technologies such as cyclotron and PET scanner. With these we can exploit the pharmacodynamics and pharmacokinetic properties in normal and diseased tissues [29].

PET imaging has an advantage that accuracy of assessing the pattern of drug deposition within the lungs In PET the actual drug molecule can be labeled by radionuclides. Carbon, Nitrogen and Oxygen are the

constituents of any organic molecules so labeling actual drug molecule is possible. The dose deposition of drug in the lungs and dose per 5-mm slice of lung tissue were analyzed by the PET images. The practical result provided a possibility of identifying the absolute doses of deposited drug and doses per unit volume of lung through the PET images. Inflammation in lungs can also be measure using the PET images by subjecting with specific markers like ^{18}FDG that can be absorbed by the inflammatory cells of the lungs [16].

HPMA (N-(2-Hydroxypropyl) methacrylamide co-polymers and their drug conjugates are the most investigated drug delivery system with various types of instruments such as SPECT, PET, and MRI. This has been used to study the pharmacokinetics and the efficiency of the HPMA co-polymers in drug targeting [30]. *In vivo* molecular imaging of the psychiatric drugs is done with the help of Positron Emission tomography (PET) and Single Photon Emission Computed Tomography (SPECT). They are used for measuring the receptors present in the range of nanomolar to the picomolar concentrations. These studies helped in the development of new drugs [31].

Due to chronic use of the opiate brain dopamine neurons are impaired. In drug carving methasone treatment is used which leads to the impairment of the dopamine neurons. To study this mechanism imaging of the dopamine receptors is done by means of PET [32].

For imaging and quantifying the molecular mechanisms of oncology in man Positron Emission Tomography was used to image the molecular pathways and interactions and provides the kinetic information. It is the most specific and sensitive imaging technique [33].
Positron Emission Tomography is a molecular imaging technique and they require some radiolabelled probes which emits positron radionuclides. Developing new probes is a challenging one and it leads to the development of new drugs [34].

MRI
Magnetic Resonance Imaging technique is used for better understanding of an object by imaging them. Forming a frame work of an object by mapping some property of that object is called as imaging. Measuring and mapping the magnetic property of an object is done by MRI. The image created by the MRI depends on the rate of magnetization of each point of an object. It is commonly used in radiology to visualize detailed internal structure and limited function of the body. It is useful for neurological imaging, musculoskeletal imaging, cardiovascular imaging and oncological imaging. Raymond vahan Damadian invented MRI scanning method and achieved life time achievement award by Lemelslon-MIT program in 2001[35].

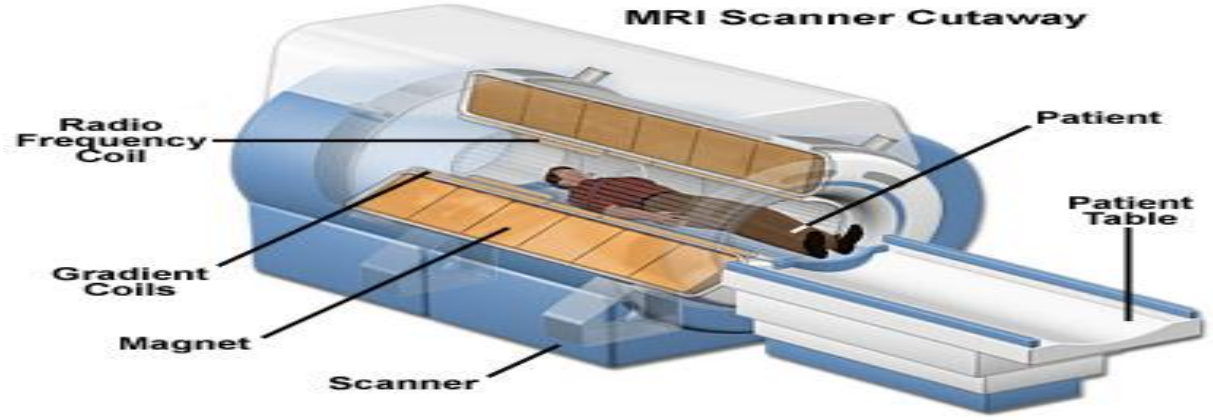

Fig 3: Magnetic Resonance Imaging

Therapeutic approaches using MRI
Nanocarrier based chemotherapy become success if only the drug extravagated across the blood brain barrier. This is said to be vascular permeability. This vascular permeability varies depending upon the tumors. A multifunctional 100 nm scale liposomal agent encapsulating the gadolinium based contrast agent for contrast enhanced magnetic resonance imaging has been developed for brain tumour therapy. The intratumoral distribution of gadolinium loaded nanocarrier in rat glioma model has been tracked using 9.4 T MRI systems [36].

To view the drug delivery by intra articular injections MRI is used. The results have proved that real time MRI is useful in achieving high rates of intra articular injections. MRI guided selective injection procedures of temporomandibular joints are safe [37].

Multifunctional micelle encoded with lung cancer targeting peptide and encapsulated with super

paramagnetic iron oxide and Doxorubicin has been used for cancer targeting and viewing the drug molecule along with the cancer. The super paramagnetic oxide and Doxorubicin facilitate the MR imaging. T2-weighted MRI is used to predict the results [38].

Using MRI analysis intra pericardial drug delivery mechanism has been done. Extracellular MRI contrast agent gadopentetate dimeglumine has been used as a model. Successful pharmacokinetic result has been obtained [39].

Biomedical imaging using MRI has been studied in mice bearing MDA-MB-231 human breast cancer xenograft. The two polymer conjugates poly (L-glutamicacid) -1, 6-hexanediamine-(Gd-DO3A) was used for the studies. Real-time and 3D visualization of blood circulation, pharmacokinetics, and tumor accumulation of conjugates and their size effects on these pharmaceutics properties has been studied using MRI [40].

In anticancer drug therapy, to check the efficiency of drug encapsulated into nano carriers' *in vitro* MRI method has been used. Through the result obtained by MRI, the diffusion of drug has been studied [41].

MRI has been used to guide the placement of catheter for local delivery of drugs. Two different image contrasts has been used to for this procedure, steady state free precession contrast was used to visualize the anatomy of the catheter and spoiled gradient echo contrast was used to view the inflow of contrasting agent. It was concluded that this technique was useful in drug delivery guided by real time MRI [42].

NIR

Near Infra Red is a spectroscopic method that uses the near infrared region of the electromagnetic spectrum to image an object is called as near infrared spectroscopy. It is used in pharmaceutical and medical diagnostic procedures. Herschel discovered this near infrared spectroscopy [43].

THERAPEUTIC APPROACHES USING NIR

For detecting, staging and monitoring of tumors, imaging with labeled monoclonal antibody will be useful. But they have a critical limiting factor. The limitation of antibody imaging is the high background signal, due to prolonged clearance from the blood that will reduce the tumor to background ratio. To overcome the problem a molecular imaging probe has been developed. It consists of multiple self quenching fluorophores [cy5.5 or Alexa flour 680 (Alexa680)] conjugated to a monoclonal antibody (tructuzumab). This conjugant will synthesize fluorescent active two components Tra-Cy5.5 (sq) or Tra-Alexa5.5 (sq) after cellular initialization. NIR spectroscopy result showed that Cy5.5-conjugates produced nonspecific results as well as rapid liver accumulation, conjugation multiple Alexa680 molecules to a single monoclonal antibody. Thus NIR imaging with labeled monoclonal antibody will be useful for characterization of tumor [44].

To characterize the epidermal growth factor receptor (EGFR) over expression during cancer development and growth, NIR is used. In Near-infrared (NIR) fluorescent dye Cy5.5-labeled anti-EFGR monoclonal antibody Erbitux is used. This can characterize EGFR expression level in MDA-MB-231 and MCF-7 breast cancer xenografts through the images obtained from NIR. The uptake of probe in EGFR-positive tumors is identified by NIR imaging [45].

To identify the degree of absorption of cic-platin an antitumor drug NIR sensitive nanoparticles has been prepared. Au-Au 2S a NIR sensitive nanoparticles were prepared by mixing HAuCl4 and Na2S in aqueous solution. The anti tumor drug was absorbed on to the prepared nanoparticle surface via the 11-mercaptoundecanoic acid layers. The drug release was sensitive to NIR irradiation [46].

NIR is used to image both *in vivo* and *ex vivo* images of the human body. The resolution can be obtained by the penetration of fluorescent lights to the human body through probes or through fluorescent dyes applied on drugs or the targeting molecules. This targeting molecule also may be a drug. The fluorescent dyes are also used to target the tumor cells [47, 48].

Angiogenesis inhibitor that weight up to 20-KD present in the C-terminal region of the collagen XVIII is the endostatin. The test conducted to verify whether the endostatin labeled with NIR probe can be useful in selective localization of tumor revealed that it will give image on NIR analysis [49].

MAGNETIC TARGETED CARRIER TECHNOLOGY

Metallic iron and activated carbon made microparticles are used as a delivery vehicle for site specific targeting, retention and release of pharmaceuticals is called as Magnetic targeted carrier (MTC). For delivering the drugs at specific targeted site of the body, MTC utilizes the physical force of magnetic field rather than using the biological metabolism.

The drugs are injected into body and guided to the target site through physical force created by magnetic field generated from the externally positioned magnet from body. Even after removing the magnetic field, the whole process results in localization and retention of delivered drug. The whole process is known as extravasaion. This technology enables decreased

exposure of the patient's body to deliver the drug but the diseased site is exposed to the drug for long duration.

Some advantages are, it will reduce the total amount of drug administration, increased concentration of desired drug can be delivered at targeted site and also side effects created by nonspecific systemic exposure can be limited. The metallic iron and activated carbon present in the MTC will not cause any side effects since these two compounds are pharmacologically active components. It contains high drug carrying capacity when compared t o other carriers.

In late 1970's Dr. Kenneth Widder and his colleagues introduced the field of magnetic targeting for drug delivery. First the practice was tested in rat tumor models with albuminmicrospheres that encase the drug and the magnetide. The magnetic albumin microspheres loaded with doxorubicin showed tumor remission activity. This has been observed as a positive result. The drug is mixed with the MTC carrier. The carbon molecule in the MTC absorbs the drug now the carrier molecule is injected in to the body via intra-arterial catheter positioned proximal. Initially MTC method has been used to cure solid tumor. Primary and metastatic liver cancers are mainly targeted. It is also used to target lung, bladder, kidney cancers sarcoma and cervical cancers using generic drugs and radionuclides attached to MTC [50].

NANOTECHNOLOGY

Nanotechnology has been developed as an effective method of drug transport and delivery system. The nanoparticles used are generally 100 nm in atleast one dimension. Different biodegradable materials such as natural or synthetic polymers, lipids or metals are present in the nanoparticles. These nanoparticles are used as drug delivery vehicles. Since these are small in size they are effectively taken by the cells .Efficient drug delivery system through nanoparticles could be achieved by understanding the following factors,

a) Pathobiology of disease
b) Molecular mechanism
c) Drug retention
d) Multiple drug administration
e) Mechanism of drug action
f) Site of drug action
g) Receptor present at the targeted site
h) Biological environment and target cell population

Antiproliferative and anti inflammatory drug Dexamethasone has been targeted by polylactic/glycolic acid (PLGA) and polylactic acid (PLA) based nanoparticles. Dexamethasone is a glucocorticoid with an intracellular site of action [51]. The drugs bind to the cytoplasmic receptor and transported to the nucleus as a drug receptor complex. To control the cell proliferation, the drug receptor complex triggers the expression of certain genes. Anticancer drug coated with nanoparticles helps the drug to effectively cross the blood brain barrier. Loperamide an antinoceceptive drug loaded in to human serum albumin nanoparticle and linked with apolipoprotein E was used in tail-flick test of mice. It showed antinoceceptive activity by recognizing the lipoprotein receptors [52].

PEBBLE (probes encapsulated by biologically localized embedding) has been developed to carry biologically active agents to their target sites. A single tiny polymer that can function against tumor has been produced. One of the molecule will guide the PEBBLE to the targeted site another molecule helps to image PEBBLE through MRI and the final molecule deliver the destructive drug to the cancer cells [53].

Amphoterisin B is an antifungal and anti-leishmanial drug. It has some toxicity in formulation. To overcome this toxisity, it has been formulated with trilaurin based nanosized lipid particles or emulsions stabilized by soya phosphatidylcholine for macrophage targeting. The drug has been delivered intravenously [54].

For targeting antileishmanial drugs into macrophages polyalkylcyanoacrylate nanoparticles has been used. The macrophages targeting procedure has been developed due to the resistance developed by the microbes against antimicrobial activity of macrophage [55].

Nanoparticles coated with αvβ3 integrin binding peptides and VEGF receptors for inhibition of tumor growth and proliferation. αvβ3 integrin and vascular endothelial growth factors plays a vital role in angiogenesis regulation. The αvβ3 integrin expressed on endothelial cells of angiogenic blood vessels bounded with synthetic polypeptide bearing Arg-Gly-Asp (RGD) sequence. This will potentially inhibit tumor growth and proliferation [56].

BIO-MEMS TECHNOLOGY

Bio-MEMS mainly used for fabrication of macromolecules to micro or nano molecules. The components that range from 1 to 100 micrometers are used to make MEMS. Silicon, Polymers and metals are some of the materials generally used to make MEMS. Bio-MEMS technology is used in medical and health related technology from lb-on-chip to micro total analysis. Some examples are biosensors, chemosensors, etc. One of the advantages of using Bio-MEMS is that, it can be made in high volume at

low cost that has pillared the use of MEMS in various fields [57].

To apply MEMS technology in medical and biology field, variety of devices are made for microfabrication. This technology includes both electronic and non electronic elements perform sensing, processing, actuation and control mechanism. It has been developed to face analytical applications. Some components for MEMS drug delivery systems are,

a) Micropump
b) Microvalve
c) Macroactuator
d) Micrineedles
e) Microreservoirs.

By the development of micro needles and immune isolation bio capsules silicon based MEMS technology has been initiated [58 - 61].

Release of specific therapeutic agents in complex dosing patterns is the main goal of MEMS in medicinal field. Hormones, chemotherapeutic agents, analgesics, anesthetics and some other bioactive components can be released [62].

Some of the complexities in MEMS drug delivery is that it should not induce the toxicity of the surrounding tissues, the drug eluting capacity of the MEMS should not be reduced by the surrounding tissues, biofouling of the nearby tissues should not occur due to the exposure of this MEMS membrane [63].
Materials used for constructing MEMS delivery systems are metallic gold, silicon, silicon dioxide, silicon nitride and SU-8^{TM} photoresist. These materials are fabricated to nano sized particles for drug delivery system. To test the complexities of MEMS delivery the system has been tested for leukocyte behavior and cellular adhesion in rat model. The results predicted that, the MEMS membrane showed biocompatible and reduced biofouling effects. It has been concluded that MEMS drug delivery using gold, silicon nitride, silicon dioxide, SU-8^{TM} is good for drug delivery mechanism [64].

LASER TECHNOLOGY

Laser has been developed in recent years for drug targeting process. It is an advanced method of drug targeting. Most probably laser technology will combine with instrumentation like Mass spectroscopy, High pressure liquid chromatography, Size exclusion chromatography, Frontal affinity chromatography, etc, to screen the interaction between drug and the target component. For the development of new therapeutic agents the main reason is the target based drug delivery system. The advent of electrospray ionization and Matrix assisted laser desorption ionization (MALDI) is for targeting the protein molecule to identify and to predict its function. This is said to be function based screening. Analyte molecules are trapped with in a porous silicon surface through a matrix-free technique called the Desorption/ionization on silicon (DIOS) time of flight technique. The analyte is absorbed and ionized by laser [65].

By this method very small amount of sample can be analyzed and also quantitative analysis can be done. For enzyme active site profiling, DIOS system can be used. A cleavable linker is present is the more delicate affinity DIOS system. This linker can be cleaved by laser pulse developed by DIOS system. The combination of this DIOS system along with tethering technology has been used for profiling enzyme active sites [66, 67].

CONCLUSION

Drug designing and non-conventional drug imaging techniques are important to image the targeted drugs in the pharmaceutical field. In addition, advanced imaging techniques such as SPECT, PET, MRI and NIR are used to image the targeted drugs in the body. Targeted drugs have to pass through specific barriers inside the body to reach target tissues or organs. Imaging the radiotracer labeled drug through SPECT and PET gives accurate and reliable measurements of targeted drug delivery. Neuroreceptor imaging in brain through PET helps to study the relationship between the dose of the targeted drug administered and the receptor occupancy of the targeted drug. In addition, some advanced technologies such as Magnetic based technology, nanotechnology, Bio-MEMS technology and laser technology also used to detect the targeted drugs. For delivering the pharmaceuticals/drugs at specific targeted site of the body, magnetic targeted carrier utilizes the physical force of magnetic field rather than using the biological metabolism and allows keeping a larger dose of the drug at the specific site (tumor) for a longer period of time, and helping protect healthy tissue. Nanotechnology has wider application for targeting the drugs with the help of natural or synthetic biopolymers. Bio-MEMS technology is used in medical and health related technology from lb-on-chip to micro total analysis. High volume low value based technology is one of the advantages to use this technique. In the Bio-MEMS technology, fabrication step is important and fabrication materials like polymer, gold, silicon are used for drug targeting and drug delivery. Laser technology is used for drug targeting, drug imaging (to image the drugs that are bound with specific analytes). The present article indicates an overview regarding the applicability of different technological advancements of different dimensions in pharmaceutical research field.

REFERENCES

[1] Drug. http://en.wikipedia/wiki/org/drug
[2] http://www.merck.com/mmhe/sec02/ch010/ch010a.html
[3] Madsen Ulf, Krogsgaard-Larsen, Povl; Liljefors, Tommy (2002). Textbook of Drug Design and Discovery, Washington, DC: Taylor & Francis.
[4] Celia M., C. Henry, E. N. Washington (2001) Structure-based drug designing. Science and technology pharmaceuticals, 79: 69-74.
[5] http://en.wikipedia.org/wiki/drug_design.
[6] http://images.apple.com/science/pdf/ligandbased_design_workfloe.pdf.
[7] http://www.magneticsmagazine.com/e-prints/ReRx.pdf.
[8] Singh M., V. Waluch (2000) Physics and instrumentation for imaging in-vivo drug distribution. Adv Drug Delivery Reviews, 41: 7-20.
[9] http://www.physics.ubc.ca/~mirg/home/tutorial/history.html.
[10] http://www.faqs.org/patents/app.
[11] http://www.reeis.usda.gov/web/crisprojectpages.
[12] YunHan L., H. Furong, L. Shiping, C Zhe (2008) Detection limit of glucose concentration with Near-infrared absorption and scattering spectroscopy. Chinese phys, 25: 1117-1119.
[13] Miller J., W. S. Wilson, W. K. Kek, C. G. Wilson, D Uttamchandani (2003) Drug detection in the living eye using a novel, minimally invasive optoelectronic system. IEEE sensors journal, 3: 95-101.
[14] http://research.microsoft.com/apps/pubs/default.
[15] Catafau A. M., M. Danus, S. Bullich, G. Nucci, J. Llop, S. Abanades, V. J. Cunningham, J. L. H. Ersels, J. Pavia, M. Farre (2006) Characterization of SPECT 5-HT2A receptor ligand 123I-R91150 in healthy volunteers: part 2-Ketanserin displacement. J Nucl Med, 47: 929-937.
[16] Dolovich M., R. Labiris (2004) Imaging drug delivery and drug responses in lungs. Proceeding of the American Thorasic society, 1: 329-337.
[17] Sasaki M., Y. Kuwabara, Y. Ichiya, T. Yoshida, M. Nakagawa, H. Soeda, K. Sugio, Y. Maehara, K. Masuda (1999) Prediction of chemosensitivity of lung cancer by 99mTc-Hexakis-2-Methoxyisobutyl Isonitrile SPECT. J Nucl Med, 40: 1778-1783.
[18] Abbott N. J., D. C. Chugani, G. Zaharchuk, R. B. Rosen, E. H. Lo (1999) Delivery of imaging agents in to brain. Adv Drug Delivery Reviews, 37: 253-277.
[19] Schmitt G. J. E., C. L. Fougere, S. Dresel, T. Frodl, K. Hahn, H. J. Moller, E. M. Meisenzahl (2007) Dual-isotope SPECT imaging of striatal dopamine: First episode drug naïve Schizophrenic patients. Schizophrenia research, 101: 133-141.
[20] Pathania D., M. Millard, N. Neamati (2009) Opportunities in discovery and delivery of anticancer drugs targeting mitochondria and cancer cell metabolism. Adv Drug Delivery Reviews, 61: 1250-1275.
[21] Watkins G. A. et al., (2009) Development of an optimized activatable MMP-14 targeted SPECT imaging probe. Bioorganic & medicinalchemistry, 17: 653-659.
[22] Wei G., H. Xu, P. T. Ding, S. M. Li, J. M. Zheng (2002) Thermosetting gels with modulated gelation temperature for ophthalmic use: the rheological and gamma scintigraphic studies. J Control Release, 83: 65-74.
[23] Pavase N., L. Kiferle, P. Piccini (2010) Neuroprotection an imaging studies in Parkinson's disease. Parkinsonism & related disorders, 15: S33-37.
[24] PET. http://en.wikipedia/wiki/org/PET.
[25] Burns H.D., T.G. Hamill, E. Waisi, B. Francis, C. Fioravanti, R. E. Gibson (1999) Positron Emission Tomography neuroreceptor imaging as a tool in drug discovery, research and development. Curr Opin Chem Biol, 3: 388-39.
[26] Kimes A. S., A. G. Horti, E. D. London, S. I. Chefer, C. Contoreggei, M. Ernst, P. Friello, A. O. Koren, V. Kurian, J. A. Matochik, O. Pavlova, D. B. Vaupel, A. G. Mukhin (2003) The FASEB J.
[27] Ou H., *et al.*, Molecular imaging of intestinal drug absorption process using Positron Emission Tomography.
[28] Roelcke U., O. Hausmann, A. Merlo, J. Missimer, R. P. Maguire, P. Freitag, E. W. Radu, R. Weinrich, O. Gratzl, K. L. Leenders (2002) PET imaging drug distribution after Intratumoral injection: The case for ^{124}I-Iododeoxyuridine in Malignant Gliomas. J Nucl Med, 43: 1444-1451.
[29] Jones T., (2005) The enabling technologies needed for PET based molecular imaging t4. support drug development. Drug Discov Today, 2: 305-309.
[30] ZhengRong L., Molecular imaging of HPMA co-polymers visualizing drug delivery in cell, mouse and man. Adv Drug Delivery Reviews. (In Press)
[31] Talbot P. S., M. Laruelle (2002) The role of In vivo molecular imaging with PET and SPECT in the elucidation of psychiatric drug and new drug development. European Neuropsycopharmacology, 12: 503-511.
[32] Shi J., Z. LiYan, L. M. Copersino, F. YuXia, Y. Chen, J. Tian, Y. Deng, Y. Shuai, J. Jin, L. Lu (2007) PET imaging of dopamine transporter and drug craving during methasone maintenance treatment and after prolonged abstinence in heroin users. Eur J Pharmacol, 579: 160-166.
[33] Price P., (2001) PET as a potential tool for imaging molecular mechanisms of oncology in man. Trends Mol Med, 7: 442-446.
[34] Serdons K., A. Verbruggen, G. M. Bormans (2009). Developing new molecular imaging probes for PET. Methods, 48: 104-111.
[35] MRI-http://en.wikipedia.org/wiki/Raymond_Vahan_Damadian.
[36] Karathanasis E et al. (2008) MRI mediated, non-invasive tracking of intratumoral distribution of nanocarriers in rat glioma. Nanotechnology, 19:
[37] Fritz J., C. Thomas, N. Tzaribachev, M. S. Horger, C. D. Claussen, J. S. Lewin, P. L. Pereria (2009) MBI-guided injection procedures of the temperomandibular joints in children and adults: Technique, accuracy and safety. AJR, 193: 1148-1154.

[38] Guthi J. S., et al. (2009) MRI visible miccelar nanomedicine for targeted drug delivery to lung cancer cells. Mol pharmaceutics (refer)

[39] Gleason J.D., K. P. Naguyen, K. V. Kissinger, W. J. Manning, R. L. Verrier (2002) Myocardial drug distribution pattern following intra pericardial delivery: An MRI analysis. J Cardiovasc Magn R, 4: 311-316.

[40] Ye F., T. Ke, E. K. Jeong, X. Wang, Y. Sun, M. Johnson, Z. R. Lu (2006) Non-invasive visualization of *in vivo* drug delivery of poly (L-glutamic acid) using contrast enhanced MRI. Mol Pharm, 3: 507-515.

[41] Lepage M., J. Jiang, J. Babin, B. Qi, Tremblay, Zhao Y. MRI observation on the light- induced release of a contrast agent from photocontrolable polymer micelles. Med boil, 52: (ref pg)

[42] Schaeffter T., S. Weiss (2004) Interactive contrast switching during real-time MRI. Proc. Intl. Soc. Mag. Reson. Med, 11: 2091.

[43] NIR- http://en.wikipedia.org/wiki/Near_infrared_spectroscopy.

[44] Ogawa M., C. A.S. Regino, P. L. Choyke, H. Kobayashi (2009) *In vivo* target specific activable near infra red optical labeling of humanized monoclonal antibodies. Mol Cancer Ther, 8: 232-239.

[45] Wang K, Wang K, Li W, Huang T, Wang D, Shen B, Chen X. 2009. Characterizing breast cancer xenograft epidermal growth factor receptor expression by using Near Infrared Optical imaging. Acta Radiol, 50: 1095-1103.

[46] Ren L., G. M. Chow NIR sensitive Au-Au_2S nanoparticles for drug delivery.

[47] Licha K., Olbrich C (2005) Optical imaging in drug discovery and diagnostic applications. Adv Drug Delivery Reviews, 57: 1807-1108.

[48] Biju V., S. Mundayoor, R. V. Omkumar, A. Anas, M. Ishikawa Bioconjucated quantum dots for cancer research: Present status, prospectus and remaining issues. Biotechnol Adv, (In Press).

[49] Citrin D., T. Scott, M. Sproull, C. Menard, P. J. Tofilon, K. Camphausen (2004) *In vivo* tumor imaging using a near-infrared-labeled endostatin molecule. Int J Radiat Oncol, 58: 536-541.

[50] http://www.magneticsmagazine.com/e-prints/ReRx.pdf.

[51] Michaleis K., M. M. Hoffmann, S. Dreis, E. Herbert, R. N. Alyautin, M. Michaleis, J. Kreuter, K. Langer (2006) Covalent linkage of apolipoprotein e to albumin nanoparticles strongly enhances drug transport in to the brain. J pharmacol Exp ther, 317: 1246-1253.

[52] Panyam J., V. Labhasetsetwar (2004) Sustained cytoplasmic delivery of drugs with intracellular receptors using biodegradable nanoparticles. Mol pham, 1: 77-84.

[53] Sumner J. P., R. Kopelman (2005) Alexa Fluor 488 as an ion sensing molecule and its applications in PEBBLE nanosensors. Analyst, 130: 528-533.

[54] Gupta S., S. P. Viyas Development and charecterization of amphotericin B bearing emulsions for passive and active macrophage targeting. J drug Target, 15: 206-217.

[55] Balland O., H. Pinto-Alphandhari, A. Viron, E. Puvion, A. Andramont, P. Couvreur (1996) Intracellular distribution of ampicillin in murine macrophages infected with *Salmonella typhimurium* and treated with (3H) ampicillin loaded nanoparticles. Journal of antimicrobial chemotherapy, 37: 105-115.

[56] Li L., C. A. Wartchow, S. N. Danthi, Z. Shen, N. Dechene, J. Pease, H. S. Chol, T. Doede, P. Chu, S. Ning, D. Y. Lee, M. D. Bednarski, S. J. Knox (2004) A novel antiangiogenesis therapy using an integrin antagonist or Anti-FIK-I antibody coated 90Y-labeled nanoparticles. Int J Radiat Oncol Biol Phy, 58: 1215-1227.

[57] MEMS - http://en.wikepedia.org/wiki/microelectromechanical_systems.

[58] Karman S., F. Ibrahim, N. Soin (2007) A review of MEMS drug delivery in medical application. IFMBE proceedings Biomed, 6: 312-315.

[59] Hernlandez P. R., C. Taboada, L. Leiia, V. Tsutsumi, B. Vlazquez, F. Valdes-peresgasga, J. L. Reyes (1998) Evaluation of biocompatibility of pH-ISFET materials during long-term subcutaneous implantation. Sens Act B, 46: 133-138.

[60] McAllister D.V., M. G. Allen, M. R. Prausnitz (2000) Microfabricated microneedles for gene and drug delivery. Annu Rev Biomed Eng. 2, 289-313.

[61] Leoni I., T. A. Desai (2001) Nanoporous biocapsules for the encapsulation of insulin cells: biotransport and biocompatibility considerations. IEEE Trans Biomed Eng, 48: 1335-1341.

[62] Anderson J. M., J. J. Langone (1999). Issues and perspectives on the biocompatibility and immunotoxicity evaluation of implanted controlled release system. J Control Release, 57: 107-113.

[63] Anderson J. M., (1996) Inflammation, wound healing and the foreign body response. Biomaterial science: an introduction to materials in medicine. San-Diego, CA; academic press Inc. chapter 4(4.2).

[64] Voskerician G., M. S. Shive, R. S. Shawgo, H. V. Recum, J. M. Anderson, M. J. Cima, R. Langer (2003) Biocompatibility and biofouling of MEMS drug delivery devices. Biomaterials, 24: 1959-1967.

[65] Thomas J. J., Z. Shen, J. E. Crowell, M. G. Finn, G. Siuzdak, Prock (2001) Disorption/ionization on silicon (DIOS): a adverse mass spectrometry platform for protein charecterisation. Proc. Natl. Acad Sci, 98: 4932-4937.

[66] Meng J. C., C. Averbuj, W. G. Lewis, G. Siuzdak, M. G. Finn (2002) Cleavable linkers for porous silicon based mass spectroscopy. Angew. Chem. Int.E, 41: 646-648.

[67] Meng J. C., G. Siuzdak, M. G. Finn (2004) Affinity mass spectroscopy from tailored porous silicon surface. Chem. Commun, 2108-2109.